J|A|C|S COMMUNICATIONS

Published on Web 12/07/2009

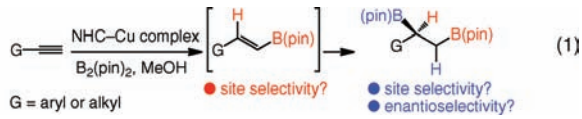
Vicinal Diboronates in High Enantiomeric Purity through Tandem Site-Selective NHC−Cu-Catalyzed Boron−Copper Additions to Terminal Alkynes

Yunmi Lee, Hwanjong Jang, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received October 21, 2009; E-mail: amir.hoveyda@bc.edu

We recently reported a site- and enantioselective Cu-catalyzed method for boron−copper addition to olefins carried out with bis(pinacolato)diboron [$B_2(pin)_2$; **1**].[1] The transformations involve N-heterocyclic carbene (NHC) complexes and are performed in the presence of MeOH, which promotes in situ protonation of the C−Cu bond to regenerate the catalyst and deliver the hydroboration product. Aryl-substituted alkenes serve as effective substrates, since a low-lying π^* orbital is likely required for association of the substrate with the nucleophilic NHC−Cu complex.[2] We reasoned that if vinylboronates can be induced to undergo site-selective hydroborations, an efficient Cu-catalyzed protocol for enantioselective synthesis of the highly versatile vicinal diboronates would be in hand.[3−5] Since vinylboronates might be prepared by alkyne hydroboration, we further envisioned a single-vessel Cu-catalyzed process for conversion of terminal alkynes to diboronates with high enantiomeric purity (eq 1).[6,7] Herein, we disclose the realization of the strategy outlined above. Through the use of a Cu complex derived from a chiral bidentate NHC,[8,9] a wide range of terminal alkynes are converted to vicinal diboronates with >98% site selectivity in 60−93% yield and up to 97.5:2.5 enantiomeric ratio (er).



(1)

We began by examining the efficiency and site selectivity of alkyne hydroboration under conditions that would likely be optimal for the second enantioselective process [−15 °C, tetrahydrofuran (thf)].[1] We established that, as illustrated in Scheme 1, reaction of Cl-substituted alkyne **2** with 5.0 mol % chiral imidazolinium salt **3** and CuCl in the presence of 20 mol % NaO*t*-Bu and 0.9 equiv of **1** leads to >98% conversion (based on **1**) in 24 h, affording vinylboronate **4** with >98% site selectivity (<2% **5** as determined by 400 MHz ^{1}H NMR analysis). Subjection of pure **4** to the same conditions (except with 1.1 equiv of **1**) furnishes diboronate **6** with >98% site selectivity (<2% geminal diboronate) in 94:6 er. As illustrated in Scheme 1, Cu-catalyzed tandem double-hydroboration of **2** with 2.1 equiv of **1** leads to 90% conversion to **6**, which is formed in 95:5 er.

In addition to terminal alkynes bearing a halogen-substituted alkyl group (Table 1, entry 1), those carrying an O- or N-based unit (entries 2 and 3) or an *n*-alkyl group (entry 4) undergo diboration to afford the desired products in 72−93% yield and up to 96.5:3.5 er. Comparison of the data in entries 5 and 6 with those in entries 7 and 8 (Table 1) indicates that transformations of alkynes containing a β-branched side chain (entries 5 and 6), where 7.5 mol % **3** is required for high conversion, proceed more slowly than those with the corresponding α-branched substituents (entries 7 and 8). In all cases, however, the desired products are isolated in 96.5:3.5 er.

The Cu-catalyzed diborations presented in eqs 2 and 3 demonstrate that the reaction can be carried out with terminal alkynes bearing a propargylic heteroatom, affording **15** and **16** in 71% and 82% yield and 97:3 and 95:5 er, respectively. These transformations, as well as those in Table 1, highlight a critical—and not immediately evident—attribute of the bidentate NHC−Cu complex derived from **3**: high site selectivity in alkyne hydroborations. This point is elucidated below.

Scheme 1. Initial Investigations

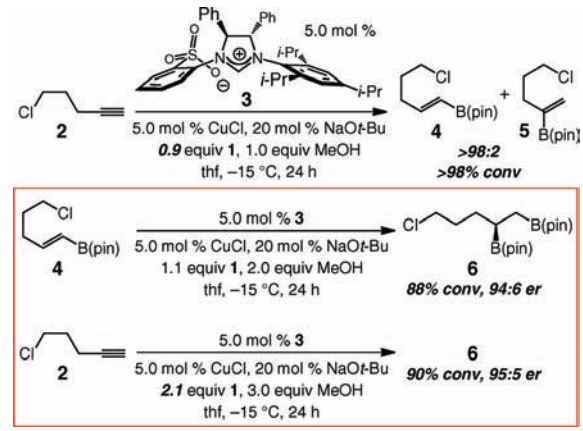
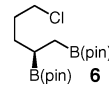
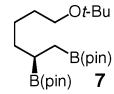
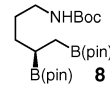
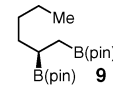
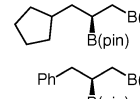
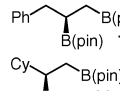
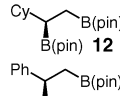
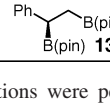


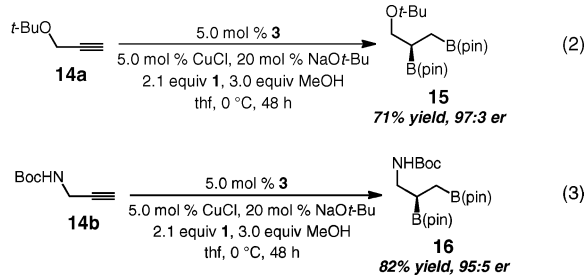
Table 1. Cu-Catalyzed Enantioselective Diboration of Terminal Alkynes[a]

entry	product	mol % **3**	conv (%);[b] diboronate (%)[b]	yield (%)[c]	er[d]
1	 **6**	5.0	>98; >98	93	94.5:5.5
2	 **7**	5.0	>98; 75	74	96.5:3.5
3	 **8**	5.0	>98; 82	72	93.5:6.5
4	 **9**	5.0	>98; 93	84	95.5:4.5
5	 **10**	7.5	>98; 81	78	96.5:3.5
6	 **11**	7.5	>98; 66	60	96.5:3.5
7	 **12**	5.0	>98; 82	76	97:3
8	 **13**	5.0	>98; 65	61[e]	97.5:2.5

[a] Reactions were performed under N_2 at −15 °C (48 h, thf), except for entry 2 (−30 °C). [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of the unpurified mixtures. [c] Yield of purified products. [d] Determined by HPLC analysis (see the Supporting Information for details). [e] Contains ∼5% geminal diboronate. B(pin) = pinacolatoboron.

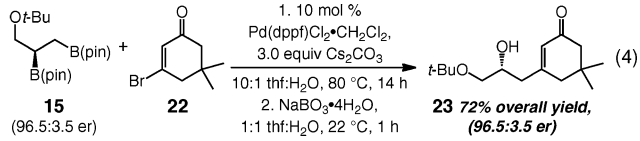
The first-stage hydroboration of alkynes **14a** and **14b** proceeds readily with 1.0 mol % monodentate NHC−Cu complex **17** (Scheme

10.1021/ja9089928

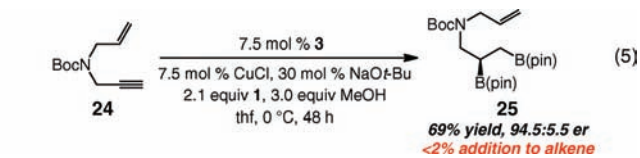


2), resulting in the formation of *secondary* vinylboronates **19a** and **19b** as the major isomers (**18**/**19** = 17:83 and 10:90, respectively). In contrast, when imidazolinium sulfonate **3** is used, **18a** and **18b** are produced predominantly (**18**/**19** = 89:11).[10] Control experiments indicate that secondary boronates (e.g., **19**) undergo Cu-catalyzed hydroboration less readily and afford products with substantially lower enantiomeric purity (with the Cu complex of **3**). For example, treatment of a pure sample of **5** with the conditions in Scheme 1 results in 13% conversion to **6**, which is formed in only 55:45 er. The high enantioselectivity afforded by the NHC−Cu complex derived from **3** is thus partly due to its ability to promote preferential formation of the terminal vinylboronates selectively. Consistent with the above findings, chiral monodentate NHC−Cu complexes **20** and **21** (Scheme 2) give rise to less efficient and nonselective transformations. The basis for the site selectivity in NHC−Cu-catalyzed alkyne hydroborations is under investigation.

The diboronates obtained through the present method are versatile, providing access to other useful enantiomerically enriched molecules. The example in eq 4 involving diboronate **15** and β-bromoenone **22** is illustrative; site-selective Pd-catalyzed cross-coupling[11] of the less hindered C−B bond followed by oxidation of the remaining alkylboronate delivers **23** in 72% yield without loss of enantiomeric purity (96.5:3.5 er).



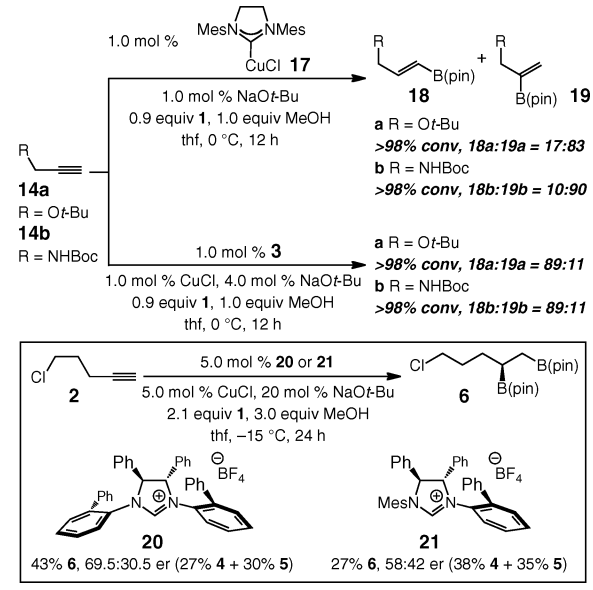
Enantiomerically enriched diboronates can be synthesized through catalytic diborations of terminal alkenes with 1 equiv of **1** or the derived biscatecholate[3,6] (vs 2 equiv as used in this study). Bis(pinacolato)diboron is, however, commercially available in ample quantities and inexpensive. The alternative protocols require the use of chiral phosphines and salts of precious metals (e.g., Pt-, Pd- or Rh-based), which are significantly more costly than CuCl. Finally, as demonstrated through the synthesis of unsaturated diboronate **25** (eq 5), the present approach complements the above-mentioned protocols involving alkene substrates;[3,6] the Cu-catalyzed reaction thus allows for chemoselective diboration of an alkyne in the presence of an olefin (<2% reaction of the alkene).



Development of other NHC−Cu-catalyzed boron−copper additions and examination of mechanistic issues are in progress.

Acknowledgment. Financial support was provided by the NSF (CHE-0715138) and the NIH (GM-47480). Y.L. is an AstraZeneca Graduate Fellow. We thank Frontier Scientific, Inc. for generous gifts of reagent **1**. The mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

Scheme 2. Influence of NHC Structure on Site Selectivity and Enantioselectivity of Boron−Copper Additions[a]



[a] Conversions for reactions with 0.9 equiv of **1** are based on the amount of this reagent and determined by ^{1}H NMR analysis. Mes = (2,4,6)-trimethylphenyl.

Supporting Information Available: Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.
(2) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443, and references cited therein.
(3) For selected reviews regarding catalytic diboron additions to alkenes (including enantioselective variants), see: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (b) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717. (c) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun.* **2009**, 3987. See the Supporting Information for additional reviews.
(4) For Rh-catalyzed enantioselective hydroborations (up to 89.5:10.5 er) of a vinylboronate [(*E*)-2-(phenylethenyl)-1,3,2-dioxaborolane], see: Wiesauer, C.; Weissensteiner, W. *Tetrahedron: Asymmetry* **1996**, *7*, 5.
(5) For Pt- and Pd-catalyzed double hydrosilylation of arylacetylenes, see: Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J. W.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 1584.
(6) For selected recent reports regarding catalytic enantioselective diboration of terminal alkenes, see: Rh-catalyzed: (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (b) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538. Pt-catalyzed: (c) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. Enantiomerically enriched diboronates have been prepared by Rh- or Ir-catalyzed hydrogenations of bisborylalkenes. See: (d) Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338. (e) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996.
(7) For a recent review of Rh- and Ir-catalyzed enantioselective alkene hydroboration, see: (a) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609. For a recent Cu-catalyzed hydroboration of monosubstituted styrenes (with pinacolborane), see: (b) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062.
(8) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorious, F., Ed.; Springer-Verlag: Berlin, 2007.
(9) For representative examples where bidentate Cu-based NHC sulfonates have been utilized in enantioselective C−C bond formation, see: (a) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904. (b) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446. For structural attributes of related Zn- and Al-based complexes, see: (c) Lee, Y.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11625.
(10) For a study regarding variations in the site selectivity of boron−copper additions to terminal alkynes (not catalytic), see: Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.
(11) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013.

JA9089928